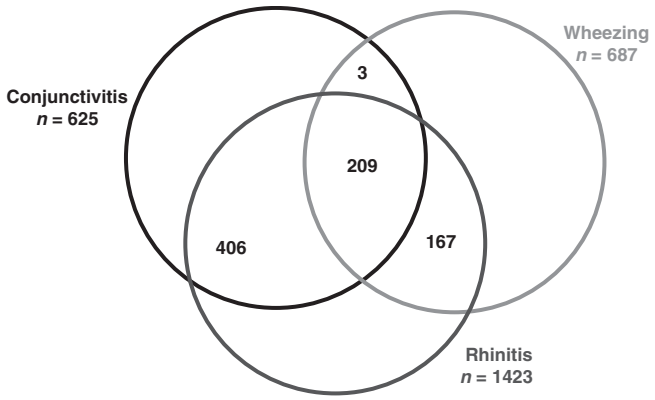

Figure 1 Relationship between conjunctivitis and allergic diseases (n = 3629).

during the last 12 months without upper airway infection (nasal pruritus, sneezing and rhinorrhoea) (2, 3).

Three thousand six hundred and twenty-nine subjects answered the written questionnaire (96% returning rate), of whom 625 (17%) presented nasal and ocular symptoms. The frequency of allergic conjunctivitis was similar between boys (48%) and girls (52%). All of the subjects with rhinitic symptoms also presented with ocular symptoms. Among patients with allergic rhinoconjunctivitis, 34% had wheezing during the last 12 months and 7% had eczema (see Fig. 1).

Seasonal rhinitis and rhinoconjunctivitis in the absence of other signs of respiratory infection are strong indicators of IgE-mediated allergy. Rhinitis as a single entity is less specific than rhinoconjunctivitis, as in addition to allergy it is often triggered by infections, air quality and physical stimuli. This may explain the divergent outcomes for rhinitis when compared with rhinoconjunctivitis. However, the prevalence of symptoms in this study was the same. It is possible that in some subjects naso-ocular reflex contributed to the ocular symptoms associated with allergic rhinitis (4). The prevalence of symptoms of allergic rhinitis and conjunctivitis was 17% in this population. In the USA, ocular allergies are estimated to affect 15–20% of the general population (5).

Response to a written questionnaire followed by a subsequent interview of 396 Swedish schoolchildren aged 12–13 years estimated the cumulative prevalence of allergic conjunctivitis of 19.1%. The prevalence of the combination of allergic conjunctivitis and allergic rhinitis was 17.6% suggesting a co-morbidity of 92% (6).

Patients with allergic rhinitis frequently present with symptoms of allergic conjunctivitis. However, terms such as hay fever or allergic rhinoconjunctivitis have been used and prevalence studies have not been specifically addressed to allergic conjunctivitis. Children with allergic conjunctivitis had other diagnosis in a secondary paediatric outpatient clinic: 97% had allergic rhinitis (7). From a pathophysiological point of view, it may be important to assess the relevance of allergic conjunctivitis for the 'one airway, one disease' concept (7). The prevalence of allergic conjunctivitis is high, as well as its association with other atopic diseases, commonly with allergic rhinitis. Focusing on conjunctivitis could improve the diagnosis of allergic rhinitis. In the ISAAC study, we missed the opportunity to assess the prevalence of conjunctivitis symptoms. If validated questions for ocular symptoms had been included, it could have facilitated the identification of the prevalence of conjunctivitis and its relationship with other allergic diseases.

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Gadoteridol-induced anaphylaxis – not a class allergy

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Keywords: gadolinium anaphylaxis; Gadoteridol; polysensitization; skin tests.

The use of gadolinium (Gd) agents for contrast-enhanced Magnetic Resonance Imaging (MRI) has increased rapidly.

Total adverse reactions range from 0.17% to 2.40%, nausea and vomiting being the most common (1). Severe anaphylactic reactions are very rare and occur in the range of 0.004–0.01% (1), mainly at first exposure. To date, few detailed reports of anaphylactic reactions related to the use of these agents have been published. In the last report (2, 3) the authors described two cases of patients polysensitized to macrocyclic gadolinium agents and postulated that a macrocyclic structure similar to the macrocyclic gadolinium chelate (gadoterate meglumine : Gd-DOTA, DOTAREM) could be the cause of a latent sensitization. Two new case reports of anaphylactic shock after first exposure to IV administration of gadolinium contrast media are detailed below. These cases do not support the 'polysensitized macrocyclic hypothesis'.

Polysensitization between gadolinium agents not always found in case of gadolinium anaphylaxis.

In case 1, a 66–year-old man with no history of allergy was referred as an outpatient for brain MRI. Shortly after an injection of Gadoteridol (Gd-HP-DO3A, PROHANCE), he presented an anaphylactic shock. He was treated with IV fluids and injections of adrenaline/epinephrine and corticosteroid before admission to an intensive care unit. Skin tests were performed in accordance to the European Network of Drug Allergy/European Academy of Allergology and Clinical Immunology recommendations. Skin prick tests (SPT) were performed with an undiluted MRI contrast agent and, when negative, were followed by intradermal tests (IDT) in the range of 10^{-3} to the undiluted commercially-available contrast media. SPT were positive with Gadoteridol at undiluted and 10^{-1} concentations and negative to Gadoterate (Gd-DOTA), Gadopentetate dimeglumine (Gd-DTPA), Gadobenate dimeglubine (Gd-BOPTA) and gadodiamide (Gd-DTPA-BMA). IDT were all positive with Gadoterate (Gd-DOTA), Gadopentetate dimeglumine (Gd-DTPA), Gadobenate dimeglubine (Gd-BOPTA) and gadodiamide (Gd-DTPA-BMA) at the undiluted concentration and all negative at the 10^{-1} concentration. Because all IDT were positive at the undiluted gadolinium contrast media, we performed them on ten exposed controls with no history of reaction to gadolinium: all SPT were negative (even at the undiluted concentrations) and half of them had positive IDT to the undiluted gadolinium agents. We therefore considered the undiluted gadolinium solutions as irritant. So, in case 1, skin tests were positive for Gadoteridol only.

In case 2, a 66-year-old man with a history of previous allergy to kiwi developed an anaphylactic shock 3 min after the second bolus of Gadobenate dimeglumine (Gd-BOPTA - MULTIHANCE) injection for whole-body MRI angiography (a first bolus was injected 15 min before). The patient had beta-blockers for cardiac disease and was successfully resuscitated by continuous IV adrenaline/epinephrine during three hours and a large IV volume expansion in intensive care. SPT were all negative with Gadoteridol (Gd-HP-DO3A), Gadoterate (Gd-DOTA), Gadopentetate dimeglumine (Gd-DTPA), Gadobenate dimeglubine (Gd-BOPTA) and gadodiamide (Gd-DTPA-BMA). IDT were positive with Gadobenate dimeglumine (Gd-BOPTA) and were all negative with Gadoterate (Gd-DOTA), Gadoteridol (Gd-HP-DO3A), Gadopentetate dimeglumine (Gd-DTPA), and gadodiamide (Gd-DTPA-BMA) at the 10^{-1} concentration. Latex IgE were negative (SPT and CAP-FEIA) (Table 1).

Our observations do not support the findings of the recent study of Hasdenteufel et al. (2, 3). First, we do not agree that the undiluted concentration of gadolinium agents is not an irritant for skin tests concerning both macrocyclic and open chain molecules. The interpretation of skin tests may not therefore be possible using this concentration. One of their two cases showed polysensitization between gadolinium agents based on a positive skin test with the undiluted concentrations. Second, our cases failed to find polysensitization between several gadolinium agents. Concerning the macrocyclic agent involved in case 1: the negativity of our SPT with Gd-DOTA does not enable us to support

Table 1 Skin test results

		Macrocyclic molecules		Open-chain molecules		
Patient	Test	Gd-DOTA Gadoterate Dotarem C=280 mg/ml	Gd-HP-DO3A Gadoteridol Prohance C=280 mg/ml	Gd-DTPA Gadopentetate dimeglumine Magnevist C=470 mg/ml	Gd-BOPTA Gadobenate dimeglumine Multihance C=530 mg/ml	Gd-DTPA-BMA Gadodiamide Omniscan C=287 mg/ml
Case 1:	SPT	– (C=undiluted)	+ ($C=10^{-1}$)	–(C=undiluted)	– (C = undiluted)	– (C=undiluted)
66 Male Gd-HP-DO3A	IDT	– ($C=10^{-1}$) + (C=undiluted)	Not done	– ($C=10^{-1}$) + (C=undiluted)	– ($C=10^{-1}$) + (C=undiluted)	– ($C=10^{-1}$) + (C=undiluted)
Case 2: 66 Male	SPT	– (C=undiluted)	– (C=undiluted)	– (C=undiluted)	– (C=undiluted)	– (C=undiluted)
Gd-BOPTA	IDT	– ($C=10^{-1}$)	– ($C=10^{-1}$)	– ($C=10^{-1}$)	+ ($C=10^{-1}$)	– ($C=10^{-1}$)

C, concentration.

the possibility of involvement of the macrocyclic structure as postulated by the authors; nevertheless this hypothesis must not be rejected and should always be checked.

Thus, all mild to severe adverse hypersensitivity reactions should be accurately documented with most of the available gadolinium in order to determine cross reactivities. This is all the more important since challenge with another gadolinium agent giving negative skin tests could be performed safely, therefore allowing these patients further MRI explorations if necessary.

This documentation should now be as rigorous as for hypersensitivity reactions associated with iodinated contrast media (4). Moreover these gadolinium reactions may be IgE-mediated more often than with iodinated contrast media because gadolinium would lead to lesser nonspecific histamine release caused by hyperosmolarity.

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Steroid dependency despite omalizumab treatment of ABPA in cystic fibrosis

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Keywords: allergic bronchopulmonary aspergillosis; cystic fibrosis; pneumonology.

Allergic bronchopulmonary aspergillosis (ABPA) occurs in 1–15% of cystic fibrosis (CF) patients and is characterized by wheezing, clinical deterioration and pulmonary infiltrates (1). Serological markers of ABPA include elevated total IgE serum levels and precipitating antibodies to *Aspergillus fumigatus* (1). The clinical course of ABPA is variable. It covers the range from a single short episode of asthma like symptoms to long-term pulmonary obstruction and corticosteroid dependency. Up to now, there are no evidence-based alternative treatment options beside steroids (2). In 2007, the first case report (3) of successful cessation of corticosteroids in the treatment of ABPA in CF with a recombinant anti-IgE antibody (omalizumab) increased expectations especially for patients with steroid-dependent ABPA.

We report of a CF patient with persistent steroid-dependent ABPA despite long-term omalizumab therapy.

More cases of CF patients with very positive outcomes of omalizumab therapy, including discontinuation of systemic corticosteroids and improvement of lung function (4, 5) have been subsequently reported.

We report the case of a 15-year-old CF patient who suffered from steroid-dependent ABPA, according to Stevens (1) criteria for 4 years with severe side-effects of long-term steroid medication, such as growth retardation. In addition to systemic corticosteroids (minimum 2.5 mg/day), she had been treated permanently with itraconazole and over a period of 12 months even with voriconazole (6) without improvement. We initiated a course of omalizumab (300 mg/4 weeks) with an forced expiratory volume in 1 s (FEV_1) of 74%, a total IgE of 248 IE/ml and 7.5 mg daily prednisolone. During the first 2 months lung function improved once to a maximum FEV_1 of 89% and the corticosteroids could be reduced to 3.75 mg/day during the following months. However, after further reduction of prednisolone to 2.5 mg, she experienced a severe relapse with a decline of FEV_1 to 55% (Fig. 1). As a result the corticosteroid dose had to be raised again. She remained steroid dependent over the full treatment period (12 months) with omalizumab (Fig. 1). Mean and best FEV_1 were in the range of the preceding 4 years, while the total steroid dose had been reduced to 90–50%.

To our knowledge, this is the first case of a long-term follow up of a CF patient with ABPA on omalizumab therapy who, after initial improvement of lung function, deteriorated again and remained steroid dependent. According to the few previous reports, it was possible to reduce corticosteroid dosage during omalizumab treatment, but in our case it could not be terminated. These earlier reports include different courses of ABPA ranging from recurrent episodes to long-term steroid dependency. As with our patient, the three cases reported by Zirbes and Milla (5) had a history of steroid-dependent ABPA for many years and omalizumab treatment was started on top of ongoing steroid medication. In these patients, the total IgE before starting the therapy was higher (ranged: 530–2894 IU/l) than in our patient. Therefore, they required higher doses of omalizumab according to the dosage recommendations. One might speculate that the higher absolute doses are a possible reason for the successful treatment in these cases.

To objectively evaluate the variety of responses to omalizumab treatment in CF patients with ABPA, it is important to add this patients' less favourable outcome to the very enthusiastic previous reports. Long-term prospective and controlled studies will help to define the cost benefit analysis of the expensive treatment of ABPA with omalizumab.